Remarks:

Claims 25-32 and 34-44 are pending in the present application. Claims 37, 38 and 40-44 are hereby cancelled. The remaining claims are generally amended to remove word redundancies in accordance with the U.S. practice. Claim 25 has an additional limitation, "said control nucleic acid consists essentially of the sequences necessary for amplification and for binding of said probe and no more than about 10% of additional nucleotides." This limitation is fully supported by the specification, see p. 7, lines 1-9. No new matter is added to the claim by these amendments. Accordingly, entry of the amendments is respectfully requested.

Claim Rejections under 35 U.S.C. §103:

Of the remaining claims, claims 25-32, 34, 35 and 39 were rejected under 35 U.S.C. §103(a) as obvious over Wittwer et al., U.S. Patent No. 6,174,670 in view of Pasloske et al. U.S. Patent No. 6,399,307. The rejection is respectfully traversed.

Wittwer teaches generally amplification and detection of nucleic acids using internally hybridized probes. The method relevant to the present invention is the use of "competitive template". In this method, the competitive template is the control nucleic acid present in the same amplification reaction and utilizing the same amplification primers and probes as the test nucleic acid[1].

However, the competitive template taught by Wittwer is patentably distinct from the control template recited in the amended claim 25. Specifically, the control template taught by Wittwer is genomic DNA. The use of genomic DNA as competitive template is described in Examples 21, 22 (Leiden mutation in the Factor V gene) and 23 (mutation in the MTHFR gene). As a control, each example uses wild-type genomic DNA without the mutation. Further, Wittwer states that genomic DNA is the desired source of control template (see col. 45, line 59). The only other type of control template taught by Wittwer is cDNA, criticized as inferior to genomic DNA (see Id.). There is no mention of using short, single-stranded DNA as a control template. Wittwer teaches that the control DNA should be as close as possible in its properties to the test DNA. Wittwer fails to recognize that a control with different properties than the test nucleic acid would also work.

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[1] The other methods taught by Wittwer, namely the use of the "positive control template" and the "reference template" involve separate amplification primers and probes for the control and the test nucleic acids. These methods are not relevant to the Applicants' invention.

Pasloske et al. teach preparation of single-stranded template: a ribonuclease-resistant RNA. One of the applications of this "Armored RNA®" is controls for quantitative amplification. However, although this control is single stranded, it is not short, like the control used in the present invention. Specifically, Armored RNA® is transcribed from a bacteriophage-based vector into which a target sequence fragment can be subcloned. Together with the bacteriophage backbone, every control sequence produced by the Pasloske method is at least 1.7 kb in length. (See col. 21, lines 57-62.) The examples from Pasloske cited by the examiner involve fragments of viral genomes inserted into the nearly full-length bacteriophage RNA. (Example II, various fragments of HIV genes; or Example V, 250 bp fragment of the HCV genome inserted into a nearly full-length bacteriophage).

As with Wittwer, these control templates are costly and time-consuming to prepare. Both Wittwer and Pasloske expend substantial efforts trying to approximate the control nucleic acid to the test nucleic acid. The Applicants discovered that the control need not mimic the test nucleic acid. The Applicants' invention teaches dispensing with long genomic DNA or elaborately-prepared long RNA. The Applicants state, "in contrast to the prior art assumptions [the control sequences] can be deleted largely or even deleted with the exception of a few nucleotides [in addition to the essential sequences]," "It is even possible that the control nucleic acid comprises exclusively, or almost exclusively, the sequence regions that hybridize with the probes and the primers." See p. 7, ¶1. In the example (starting on p. 10, l. 23), the Applicants teachings are validated when the test nucleic acid, Hepatitis B (HBV) DNA (3.2 kb) from an infected patient's blood, is successfully used with a single-stranded 120-base-long DNA control.

Based on the prior art teachings, substituting short single-stranded polynucleotide for thousands of bases or base pairs-long polynucleotide is not obvious. A person of ordinary skill could not have predicted that the strategy would work. Based on Wittwer and Pasloske, the control template should be as close as possible in size and property to the test template. Therefore mammalian genomic DNA should be used with mammalian genomic DNA control and several kilobases-long viral nucleic acid should be used with a several kilobases-long viral nucleic acid control. The Applicants disclose a radically new solution to the problem: regardless of the test nucleic acid, one may use a short, single stranded DNA that contains little more than the sequences essential for amplification and detection.

Because the substitution described above would not have been obvious to a person of ordinary skill, rejection of claim 25 as obvious over Wittwer in view of Pasloske may not

be sustained. Accordingly, reconsideration and withdrawal of the rejection of claim 25 under 35 U.S.C. §103(a) are respectfully requested.

The remaining claims depend ultimately on claim 25, and therefore incorporate all the limitations of that claim. Specifically, each of the pending claims 26-32, 34, 35 and 39 requires the use of the novel and non-obvious control nucleic acid, not disclosed or suggested by Wittwer, Pasloske or the combination of the two. Accordingly, withdrawal of the rejections of the dependent claims over Wittwer and Pasloske are respectfully requested.

Conclusion:

In view of the above, Applicants believe that all claims now pending in this application are in condition for allowance. The Commissioner is authorized to charge a one-month extension of time fee (large entity) and any additional fee deficiency, or credit any overpayment, to Deposit Account No. 50-0812.

If the Examiner believes that a telephone conference would expedite prosecution of this application, the examiner is invited to call the undersigned directly at 510-814-2706.

Respectfully submitted,

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